UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/693,558	10/20/2000	Elfi Biedermann	25846-0003	7777

25213 7590 07/08/2008

HELLER EHRMAN LLP
4350 La Jolla Village Drive, 7th Floor
San Diego, CA 92122

EXAMINER	
ANDERSON, JAMES D	
ART UNIT	PAPER NUMBER
1614	

MAIL DATE	DELIVERY MODE
07/08/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/693,558	BIEDERMANN ET AL.	
	Examiner	Art Unit	
	JAMES D. ANDERSON	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 March 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *57-82* is/are pending in the application.

4a) Of the above claim(s) *65 and 72-82* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *57-64 and 66-71* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 57-82 are presented for examination

Applicants' response filed 3/3/2008 has been received and entered into the application. No claims are amended, cancelled, or added. Claims 65 and 72-82 remain withdrawn from consideration.

Applicants' arguments have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

In light of the new rejections being applied against the pending claims, this Office Action is **Non-Final**.

Response to Arguments

Applicant's arguments with respect to claims 57-64 and 66-71 have been considered but are moot in view of the new ground(s) of rejection.

Claim Rejections - 35 USC § 112 (1st Paragraph)

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 57-64 and 66-71 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which

was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a Written Description rejection.

The instant claims recite "a compound having vitamin PP activity or *an ester thereof*". There is insufficient written description for esters of compounds having vitamin PP activity.

Regarding the requirement for adequate written description of chemical entities, Applicant's attention is directed to the MPEP §2163. In particular, *Regents of the University of California v. Eli Lilly & Co*., 119 F.3d 1559, 1568 (Fed. Cir. 1997), *cert. denied*, 523 U.S. 1089, 118 S. Ct. 1548 (1998), holds that an adequate written description requires a precise definition, such as by structure, formula, chemical name, or physical properties, "not a mere wish or plain for obtaining the claimed chemical invention." *Eli Lilly*, 119 F.3d at 1566. The Federal Circuit has adopted the standard set forth in the Patent and Trademark Office ("PTO") Guidelines for Examination of Patent Applications under the 35 U.S.C. 112.I "Written Description" Requirement ("Guidelines"), 66 Fed. Reg. 1099 (Jan. 5, 2001), which state that the written description requirement can be met by "showing that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics," including, *inter alia*, "functional characteristics when coupled with a known or disclosed correlation between function and structure..." *Enzo Biochem, Inc. v. Gen-Probe Inc*., 296 F.3d 316, 1324-25 (Fed. Cir. 2002) (quoting *Guidelines*, 66 Fed. Reg. at 1106 (emphasis added)). Moreover, although *Eli Lilly* and *Enzo* were decided within the factual context of DNA sequences, this does not preclude extending the reasoning of those cases to chemical structures in general. *Univ. of Rochester v. G.D. Searle & Co*., 249 Supp. 2d 216, 225 (W.D.N.Y. 2003).

Applicants have failed to provide any structural characteristics, chemical formula, name(s) or physical properties, aside from recitation of "esters thereof", that would provide adequate written description of the genus of esters of compounds having vitamin PP activity. Absent an adequate written description of such esters of compounds having vitamin PP activity, it is not apparent that Applicants were actually in possession of, and intended to be used within the context of the present invention, any esters of compounds having vitamin PP activity. While Applicants disclose the structures of compounds of formulas II, IIa, IIb, III, IIIa, IIIb, IIIc, IV, IVa, IVb, V, Va, and Vb, nowhere do Applicants disclose any esters of such compounds.

Claims 66-67 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a Written Description rejection.

The instant claims recite "a compound having vitamin PP activity or an ester thereof". There is insufficient written description for compounds having vitamin PP activity, other than compounds of formula II, IIa, IIb, III, IIIa, IIIb, IIIc, IV, IVa, IVb, V, Va, and Vb.

Regarding the requirement for adequate written description of chemical entities, Applicant's attention is directed to the MPEP §2163. In particular, *Regents of the University of California v. Eli Lilly & Co.*, 119 F.3d 1559, 1568 (Fed. Cir. 1997), *cert. denied*, 523 U.S. 1089, 118 S. Ct. 1548 (1998), holds that an adequate written description requires a precise definition, such as by structure, formula, chemical name, or physical properties, "not a mere wish or plain

for obtaining the claimed chemical invention." *Eli Lilly*, 119 F.3d at 1566. The Federal Circuit has adopted the standard set forth in the Patent and Trademark Office ("PTO") Guidelines for Examination of Patent Applications under the 35 U.S.C. 112.I "Written Description" Requirement ("Guidelines"), 66 Fed. Reg. 1099 (Jan. 5, 2001), which state that the written description requirement can be met by "showing that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics," including, *inter alia*, "functional characteristics when coupled with a known or disclosed correlation between function and structure..." *Enzo Biochem, Inc. v. Gen-Probe Inc*., 296 F.3d 316, 1324-25 (Fed. Cir. 2002) (quoting *Guidelines*, 66 Fed. Reg. at 1106 (emphasis added)). Moreover, although *Eli Lilly* and *Enzo* were decided within the factual context of DNA sequences, this does not preclude extending the reasoning of those cases to chemical structures in general. *Univ. of Rochester v. G.D. Searle & Co*., 249 Supp. 2d 216, 225 (W.D.N.Y. 2003).

Applicants have failed to provide any structural characteristics, chemical formula, name(s) or physical properties, aside from compounds of formula II, IIa, IIb, III, IIIa, IIIb, IIIc, IV, IVa, IVb, V, Va, and Vb, that would provide adequate written description of the genus of compounds having vitamin PP activity. Absent an adequate written description of such compounds having vitamin PP activity and esters thereof, it is not apparent that Applicants were actually in possession of, and intended to be used within the context of the present invention, any other compounds having vitamin PP activity, other than those of formula II, IIa, IIb, III, IIIa, IIIb, IIIc, IV, IVa, IVb, V, Va, and Vb as disclosed in the specification.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

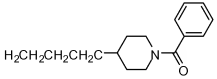
> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 57-64 and 66-71 are rejected under 35 U.S.C. 103(a) as being unpatentable over **WO 97/48397** (Published December 24, 1997) (prior art of record) in view of **Hoskin *et al***. (British Journal of Cancer, 1997, vol. 76, pages 260-263) (newly cited – Abstract attached).

The instant claims recite pharmaceutical compositions comprising a compound of Formula (I), *e.g.*, N-[4-(1-benzoylpiperidin-4-yl)-butyl]-3-(pyridin-3-yl)-acrylamide, and a compound having vitamin PP activity, *e.g.*, a compound of Formula II, IIa, IIb, III, IIIa, IIIb, IIIc, IV, IVa, IVb, V, Va, or Vb. Such compounds of Formula V include the instantly elected nicotinamide.

WO '397 teaches compounds of Formula (I) for use in the treatment of tumors or for immunosuppression (Abstract). The compounds of Formula (I) are defined at pages 3-13 of WO

'397 and include the instantly elected N-[4-(1-benzoylpiperidin-4-yl)-butyl]-3-(pyridin-3-yl)-acrylamide as recited in instant claim 58 when R^1 is H, k is 0, A is CH_2=CH_2, R^4 is H, and D-E-G is  (Compound No. 259 in Table 2 of WO '397). With regard to the administration forms as recited in claims 69-71, WO '397 teaches the same administration forms at pages 178-187. The compounds of Formula (I) as disclosed in WO '397 can be combined with other chemotherapeutic agents (page 204) as well as with radiotherapy, hyperthermia, or immunotherapy (pages 204 and 206). The inventors also teach that the compositions and methods of the invention are not limited to the respective "concretely named" active ingredient concentrations, dosages, combinations with one or more other cytostatic agents, tumor inhibitors, cancerostatic agents, immunosuppressive agents or further medicinal agents suitable for the respective specific indications or the type of tumor to be treated or immunological illness (page 206).

What WO '397 does not explicitly teach is the specific combination of a compound of Formula (I) (*e.g.*, N-[4-(1-benzoylpiperidin-4-yl)-butyl]-3-(pyridin-3-yl)-acrylamide) and a vitamin PP active agent (*e.g.*, nicotinamide) as recited in the instant claims.

However, Hoskin *et al*. teach administration of nicotinamide and nicotinamide + carbogen to patients having bladder cancer undergoing radiation therapy (Abstract). The clinical results show that carbogen and nicotinamide may improve the results of daily fractionated radiotherapy in bladder cancer.

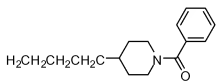
Accordingly, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to formulate a composition comprising a compound of Formula

(I) as taught in WO '397 and nicotinamide as taught in Hoskin *et al*. The inventors of WO '397 clearly suggest and motivate combinations of compounds of Formula (I) with other chemotherapeutic agents (page 204) as well as with radiotherapy, hyperthermia, or immunotherapy (pages 204 and 206). Hoskin *et al*. clearly teach that nicotinamide is useful when used in combination with radiotherapy for the treatment of bladder cancer. As such, one of ordinary skill in the art at the time the invention was made would have been imbued with at least a reasonable expectation that a composition comprising a compound of Formula (I) and nicotinamide would be effective in treating bladder cancer when used in combination with radiotherapy. It is noted that WO '397 teaches that the compounds of the invention and their salts have therapeutic use in the treatment of solid tumors such as bladder tumors (page 203).

Claims 57-64 and 66-71 are rejected under 35 U.S.C. 103(a) as being unpatentable over **WO 97/48397** (Published December 24, 1997) (prior art of record) in view of **Olsson *et al***. (British Journal of Cancer, 1996, vol. 74, pages 368-373) (newly cited – Abstract attached).

The instant claims recite pharmaceutical compositions comprising a compound of Formula (I), *e.g*., N-[4-(1-benzoylpiperidin-4-yl)-butyl]-3-(pyridin-3-yl)-acrylamide, and a compound having vitamin PP activity, *e.g*., a compound of Formula II, IIa, IIb, III, IIIa, IIIb, IIIc, IV, IVa, IVb, V, Va, or Vb. Such compounds of Formula V include the instantly elected nicotinamide.

WO '397 teaches compounds of Formula (I) for use in the treatment of tumors or for immunosuppression (Abstract). The compounds of Formula (I) are defined at pages 3-13 of WO '397 and include the instantly elected N-[4-(1-benzoylpiperidin-4-yl)-butyl]-3-(pyridin-3-yl)-

acrylamide as recited in instant claim 58 when R^1 is H, k is 0, A is CH_2=CH_2, R^4 is H, and D-E-G is  (Compound No. 259 in Table 2 of WO '397). With regard to the administration forms as recited in claims 69-71, WO '397 teaches the same administration forms at pages 178-187. The compounds of Formula (I) as disclosed in WO '397 can be combined with other chemotherapeutic agents (page 204) as well as with radiotherapy, hyperthermia, or immunotherapy (pages 204 and 206). The inventors also teach that the compositions and methods of the invention are not limited to the respective "concretely named" active ingredient concentrations, dosages, combinations with one or more other cytostatic agents, tumor inhibitors, cancerostatic agents, immunosuppressive agents or further medicinal agents suitable for the respective specific indications or the type of tumor to be treated or immunological illness (page 206).

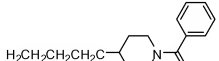
What WO '397 does not explicitly teach is the specific combination of a compound of Formula (I) (*e.g.*, N-[4-(1-benzoylpiperidin-4-yl)-butyl]-3-(pyridin-3-yl)-acrylamide) and a vitamin PP active agent (*e.g.*, nicotinamide) as recited in the instant claims.

However, Olsson *et al*. teach that nicotinamide induces DNA damage and repair when administered to mice inoculated with adenotype 12 virus-induced mouse sarcoma A12B3 and sarcoma F (Abstract). Administration of between 100 and 1000 mg/kg nicotinamide causes a high level of *in vivo* DNA strand breaks in tumors and in normal tissues in mice bearing the immunogenic sarcoma A12B3. Nicotinamide also delayed the repair process of DNA strand breaks (Abstract).

Accordingly, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to formulate a composition comprising a compound of Formula (I) as taught in WO '397 and nicotinamide as taught in Olsson *et al*. The inventors of WO '397 clearly suggest and motivate combinations of compounds of Formula (I) with other chemotherapeutic agents (page 204) as well as with radiotherapy, hyperthermia, or immunotherapy (pages 204 and 206). Olsson *et al*. clearly teach that nicotinamide induces DNA damage and delays DNA repair when administered to mice bearing immunogenic sarcoma A12B3. As such, one of ordinary skill in the art at the time the invention was made would have been imbued with at least a reasonable expectation that a composition comprising a compound of Formula (I) and nicotinamide would be effective in treating a sarcoma by inducing DNA damage and inhibiting DNA repair. It is noted that WO '397 teaches that the compounds of the invention and their salts have therapeutic use in the treatment of soft tissue sarcomas (page 203).

Claims 57-64 and 66-71 are rejected under 35 U.S.C. 103(a) as being unpatentable over **WO 97/48397** (Published December 24, 1997) (prior art of record) and **Pero** (USP No. 5,340,565; Issued Aug. 23, 1994) (newly cited).

The instant claims recite pharmaceutical compositions comprising a compound of Formula (I), *e.g.*, N-[4-(1-benzoylpiperidin-4-yl)-butyl]-3-(pyridin-3-yl)-acrylamide, and a compound having vitamin PP activity, *e.g.*, a compound of Formula II, IIa, IIb, III, IIIa, IIIb, IIIc, IV, IVa, IVb, V, Va, or Vb. Such compounds of Formula V include the instantly elected nicotinamide.

WO '397 teaches compounds of Formula (I) for use in the treatment of tumors or for immunosuppression (Abstract). The compounds of Formula (I) are defined at pages 3-13 of WO '397 and include the instantly elected N-[4-(1-benzoylpiperidin-4-yl)-butyl]-3-(pyridin-3-yl)-acrylamide as recited in instant claim 58 when R^1 is H, k is 0, A is CH_2=CH_2, R^4 is H, and D-E-G is  (Compound No. 259 in Table 2 of WO '397). With regard to the administration forms as recited in claims 69-71, WO '397 teaches the same administration forms at pages 178-187. The compounds of Formula (I) as disclosed in WO '397 can be combined with other chemotherapeutic agents (page 204) as well as with radiotherapy, hyperthermia, or immunotherapy (pages 204 and 206). The inventors also teach that the compositions and methods of the invention are not limited to the respective "concretely named" active ingredient concentrations, dosages, combinations with one or more other cytostatic agents, tumor inhibitors, cancerostatic agents, immunosuppressive agents or further medicinal agents suitable for the respective specific indications or the type of tumor to be treated or immunological illness (page 206).

What WO '397 does not explicitly teach is the specific combination of a compound of Formula (I) (*e.g.*, N-[4-(1-benzoylpiperidin-4-yl)-butyl]-3-(pyridin-3-yl)-acrylamide) and a vitamin PP active agent (*e.g.*, nicotinamide) as recited in the instant claims.

However, Pero teaches methods of inhibiting or killing tumor or cancer cells in a patient comprising administering "a chemotherapeutic agent" in combination with nicotinamide and an oxidative stressing agent (see claim 6 of Pero). Nicotinamide has been shown to be an effective

sensitizer of the cytotoxic action of induced by radiation and cancer chemotherapeutic drugs (col. 2, lines 21-46).

Accordingly, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to formulate a composition comprising a compound of Formula (I) as taught in WO '397 and nicotinamide as taught in Pero. The inventors of WO '397 clearly suggest and motivate combinations of compounds of Formula (I) with other chemotherapeutic agents (page 204) as well as with radiotherapy, hyperthermia, or immunotherapy (pages 204 and 206). Pero clearly suggests that compositions comprising a chemotherapeutic agent, nicotinamide, and an oxidative stressing agent can be used to treat cancer in human patients. As such, one of ordinary skill in the art at the time the invention was made would have been imbued with at least a reasonable expectation that a composition comprising a compound of Formula (I), nicotinamide, and an oxidative stressing agent would be effective in inhibiting or killing tumor or cancer cells in a patient. It is noted that both WO '397 and Pero suggest combination therapy comprising the compounds instantly claimed.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JAMES D. ANDERSON whose telephone number is (571)272-9038. The examiner can normally be reached on MON-FRI 9:00 am - 5:00 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/James D Anderson/
Examiner, Art Unit 1614

/Ardin Marschel/
Supervisory Patent Examiner, Art Unit 1614